REMARKS

INTRODUCTORY REMARKS

Applicants respectfully request entry of the amendments and remarks from applicant's September 3, 2009 Reply with this request for continued examination.

Following entry of this amendment, claims 56, 69-71, and 78 are pending and claims 1-55, 57-68, 72-77 are canceled.

THE CLAIM AMENDMENTS

Applicants have canceled claim 76. Applicants have canceled this claim without prejudice or waiver of applicants' right to file for and obtain claims directed to any canceled subject matter in this application or in divisional or continuing applications claiming priority from this application.

Applicants have amended claim 56 to improve its form. Specifically, applicants have amended claim 56 to recite specific ACE inhibitors and to specify that the ACE inhibitor is at a concentration effective to synergistically stimulate the ability of the BMP morphogen to reduce proteinuria levels in a patient having diabetic nephropathy. Support for this amendment may be found, for example, at specification page 98, line 20 – page 99, line 5 and page 142, line 18 – page 143, line 14.

Applicants have amended claim 78 to remove its dependency from canceled claim 76.

None of the amendments introduces any new matter.

THE REJECTIONS

Claim rejection under 35 U.S.C. § 103(a)

Claims 56, 70-71, 76 and 78

In the September 29, 2009 Advisory Action, the Examiner maintained the rejection of claims 56, 70-71, 76 and 78 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent 6,498,142 ("Sampath") and London et al., Journal of Hypertension, 14:1139-1146 (1996) ("London"). As discussed in the July 6, 2009 Final Office Action, the Examiner contends that Sampath discloses that OP-1 successfully attenuates renal failure in an art-accepted model for renal failure and that London teaches the administration of ACE inhibitors for the treatment of hypertensive subjects with end stage renal disease. The Examiner concludes that both OP-1 and ACE inhibitors are used to treat the same patient population (patients with renal disease) and that the skilled worked would be motivated to apply OP-1 and ACE inhibitors to individuals with renal disease, as evidenced by Ritz, Am. J. Hypertension, 8:53S-58S (1995) ("Ritz") and de Zeeuw et al., Canadian Journal of Cardiology, 11(Suppl.F):41F-44F (1995) ("de Zeeuw").

The Examiner further contends in the Advisory Action that *In re Soni*, 34 U.S.P.Q. 2d. 1684 (Fed. Cir. 1995) fails to rebut a *prima facie* case of obviousness. Specifically, the Examiner states that *In re Soni* is distinguishable from the instant application because (1) it is directed to product by process claims that result in a physical/structural difference that imparts greater tensile strength; (2) the claims recite a specific molecular weight of the polymer; and (3) the only remarks made in *In re Soni* with regard to synergism were found in the dissenting opinion. The Examiner states that in contrast to *In re Soni*, the instant claims are drawn to broad compositions already

known in the art (any BMP and any ACE inhibitor) that when administered together improve proteinuria in a synergistic fashion. Applicants traverse.

Applicants have canceled claim 76, thus rendering the rejection moot with respect to that claim.

With respect to the remaining claims, applicants respectfully submit that they are not obvious over Sampath and London (as further evidenced by Ritz and de Zeeuw). Nonetheless, solely to expedite prosecution, applicants have amended claim 56 (and therefore, dependent claims 70-71, and 78) to specify that the ACE inhibitor is selected from the group consisting of enalapril, lisinopril, quinapril, ramipril, ciliazapril and benazapril and that the ACE inhibitor is at a concentration effective to synergistically stimulate the ability of the BMP morphogen to reduce proteinuria levels in a patient having diabetic nephropathy. Nothing in Sampath, London, Ritz and de Zeeuw, either alone or in combination, renders the amended claims of the instant application obvious.

Applicants submit that nowhere in any of Sampath, London, Ritz and de Zeeuw is there any teaching or suggestion to combine a BMP and an ACE inhibitor, let alone, to combine an ACE inhibitor selected from the Markush group of inhibitors wherein the ACE inhibitor is at a concentration effective to synergistically stimulate the ability of the BMP morphogen to reduce proteinuria.

Applicants submit that the specifically recited ACE inhibitors -- enalapril, lisinopril, quinapril, ramipril, ciliazapril and benazapril -- are structurally related inhibitors and would exhibit similar functional activity. *See*, Kostis, Journal of Human Hypertension, 3(Suppl.1):119-125 (1989), Table I, attached herein as Exhibit A. Applicants submit that although the specification

demonstrates the effect of enalapril with OP-1(as the BMP), one of ordinary skill in the art would appreciate that any of the other recited ACE inhibitors would act in a similar manner. Moreover, the amended claims require the specific ACE inhibitor to be at a concentration which results in synergy with the BMP morphogen to reduce proteinuria levels in a patient having diabetic nephropathy. Thus, only those recited ACE inhibitors that are present at those concentrations that are effective to synergistically stimulate the ability of the BMP morphogens to reduce proteinuria levels are claimed. This feature is also nowhere taught or suggested in any of the references.

Furthermore, applicants submit that *In re Soni* supports the rebuttal of the *prima facie* case of obviousness in the instant application. *In re Soni* indicates that a showing of unexpected results is "to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Id.* at 1687. The synergy that results from the claimed combination of a BMP and the specifically recited ACE inhibitors is clearly a superior property or advantage. Moreover, applicants have demonstrated that the synergistic property of the reduced proteinuria levels was surprising or unexpected. *See*, Example 4, specification pages 142-143.

Thus, based on the state of the art, the skilled worker would not have been motivated to combine any of the specifically recited ACE inhibitors with a BMP morphogen to reduce proteinuria. Nor would the skilled worker have expected that the combination would result in a synergistic effect. For all of the above reasons, applicants submit that the amended claims of the instant application are not obvious and request that the Examiner withdraw this rejection.

Claim 69

The Examiner has maintained the rejection of claim 69 under 35 U.S.C. § 103(a) as being obvious over Sampath, London and Salvetti et al., Drugs, 40:800-28 (1990) ("Salvetti") for the reasons of record in the July 6, 2009 Final Office Action. The Examiner states that Sampath and London do not teach that the ACE inhibitor is enalapril but that Salvetti reviews and compares ACE inhibitors including enalapril. The Examiner further states that Salvetti teaches that enalapril is more potent and has a longer duration of action. The Examiner concludes that the skilled worker would be motivated to use enalapril because of the greater potency and duration and could have reasonably expected success. Applicants traverse.

As discussed above, nothing in Sampath or London, either alone or in combination, teaches or suggests combining the specifically recited ACE inhibitors with a BMP morphogen to reduce proteinuria levels or that the combination would have a synergistic effect on reducing proteinuria levels. Salvetti does not remedy this deficiency. Salvetti only discloses that enalapril is more potent and has longer duration of action than other ACE inhibitors. That disclosure in no way would motivate the skilled worker to combine enalapril with BMPs to synergistically reduce proteinuria levels. Therefore, the combination of Sampath, London and Salvetti does not render claim 69 obvious for the same reasons that the combination of Sampath and London does not render the claim obvious. Accordingly, applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

In view of the foregoing remarks, applicants request that the Examiner reconsider and withdraw all outstanding rejections and allow the pending claims.

The Examiner is invited to telephone applicants' representatives regarding any matter that may be handled by telephone to expedite allowance of the pending claims.

Respectfully submitted,

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Exhibit A

Journal of Human HYPERTENSION

ACE Inhibition—The Next Decade

Focus on Lisinopril

Volume 3 Supplement 1 June 1989

Journal of Human
HYPERTENSION

Volume 3 Supplement 1 June 1989

ACE INHIBITION — THE NEXT DECADE

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CONCLUDING REMARKS

The contribution of Dr H.A. Cameron, Senior Medical Advisor, ICI Pharmaceuticals, Macclesfield, UK, is gratefully acknowledged.

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Pharmacological differentiation of angiotensin-converting enzyme inhibitors

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Summary: **Drugs within the ACE inhibitor class may be differentiated by criteria related to chemical structure, potency, metabolism, and pharmacokinetics. Duration of action, the relationship between chemical structure and clinical activity, and the need for bioactivation currently represent the most clinically relevant differences amongst the ACE inhibitor class.**

Introduction

ACE inhibitors were introduced into clinical practice 10 years ago and are widely prescribed for the treatment of hypertension and congestive heart failure (CHF).[1–3] In 1988, sales of two agents in this drug class exceeded one billion US dollars each. The commercial success of ACE inhibitors, based on their therapeutic efficacy, paucity of significant side effects, and emerging new indications, has created much interest in the synthesis and development of new compounds.[4–7] More than 50 molecules with ACE inhibitory activity and potential for clinical application have been synthesised, and more than 10 are now in clinical development worldwide.[4–8]

The increasing number of these compounds has made it necessary to classify them and delineate differences.[8–10] Table I contains a classification according to their origin and chemical structure. Most ACE inhibitors of potential clinical value are synthetic peptide analogues. These compounds, usually dipeptide or tripeptide analogues, can be further classified according to the moiety that functions as the zinc ligand. This moiety is the sulphydryl group for captopril, a carboxyl group for most other ACE inhibitors in use or in development, and phosphinyl for fosinopril.

Although the ACE inhibitors share similar general properties and do not differ markedly in their clinical utility, differences amongst them are becoming apparent. A list of these is presented in Table II. Among the properties used to differentiate ACE inhibitors, some are of theoretical rather than practical importance at the present time, while others are clinically relevant.

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Chemical class

Chemical class is an important dimension for differentiating ACE inhibitors since it determines many of their properties. In particular, considerable attention has been paid to the presence or absence of the sulphydryl (–SH) moiety. During the original synthesis of the first clinically useful oral ACE inhibitor (captopril), the sulphydryl group was inserted in order to increase the potency of the compound. It was noted that substitution of a sulphydryl for the carboxyl group of a chemical precursor of captopril results in increased potency because of the strong binding of the sulphydryl group to the zinc atom of the converting enzyme. Of the compounds currently marketed, only captopril contains a sulphydryl group.

Initially, captopril was administered at a high dose level to patients refractory to other forms of treatment, and it was associated with a significant incidence of serious side effects. The sulphydryl group was widely implicated as a potential mediator of these adverse effects. The side effects of captopril and other sulphydryl-containing compounds have been reviewed by Jaffe and include leucopenia, taste disturbance, skin rashes, proteinuria, neutropenia and oral ulcers.[11] Subsequent use of captopril at lower doses and in patients without collagen disease or renal failure has demonstrated that this agent is remarkably safe and not associated with a decline in renal function or autoim-

Table I Classification of ACE inhibitors.

I. Natural
- *a.* Peptides
  1. snake (e.g. teprotide, BPP_{5a})
  2. human (e.g. enkephalins, substance P)
  3. microbial (e.g. ancovenin, muracein)
- b. Non-peptides (e.g. bicyclic lactams)

II. Synthetic
- a. Peptides (e.g. phe-ala-pro)
- b. Peptide analogues (di- or tri-peptide)
  1. Sulphur as zinc ligand (e.g. alacepril, captopril, pentiapril, pivalopril, zofenopril)
  2. Carboxyl as zinc ligand (e.g. benazepril, cilazapril, delapril, enalapril, lisinopril, perindopril, quinapril, ramipril)
  3. Phosphinyl as zinc ligand (e.g. fosinopril)
- c. Angiotensin I analogues (e.g. phosphonic acid replacing C-terminal COOH)
- d. Peptide surrogates (tri- or pentapeptides) ester or ketomethyl, $-COSCH_2-$ as substitutes for peptide bond [CONH]

(Modified from Kostis & DeFelice.[3])

mune disorders in this patient subset. Nevertheless, even when used at low doses and with careful patient selection, taste disturbances and skin rashes are more common in patients receiving captopril than in those treated with non-sulphydryl-containing ACE inhibitors.[6] These are dose-dependent effects which tend to occur early after the initiation of treatment, and do not always necessitate discontinuation of the medication. The mechanism underlying the rash is not well understood, but has been attributed to allergic reactions or to increased kinin and prostaglandin production.[6]

Since the sulphydryl group in captopril is not essential to its ACE inhibitory activity, one might consider drugs with this moiety as having two properties; that is ACE inhibitory activity, in common with non-sulphydryl ACE inhibitors, and properties related to the sulphydryl group which may confer either side effects or beneficial effects. For example, prostaglandin levels may increase during ACE inhibitor treatment by two mechanisms: activation of phospholipase by an increased concentration of kinins (due to decreased kinin degradation by ACE, an effect shared by all ACE inhibitors) or by direct activation of phospholipase by the sulphydryl group. This enhancement of prostaglandin production has been linked with both beneficial and adverse drug effects.

Taste disturbance associated with captopril is

Table II ACE inhibitor differentiation.

1. Chemical class
   e.g. zinc ligand (–SH)
2. Prodrugs
   site and time course of bioactivation
3. Potency
   K_i
   IC_{50}
   Radioligand binding displacement
4. Pharmacokinetics
   absorption, duration of action, bioavailability, distribution, metabolism, excretion, protein binding, etc.
5. Tissue effects
   lipophilicity
   tissue penetration, time couse, dissociation constants, etc.
6. Side effects
7. Additional pharmacological properties (e.g. diuretic activity)
8. Drug interactions
9. Cost

(Modified from Kostis & DeFelice.[3])

usually dysgeusia or hypogeusia. Objective testing has shown an increase in the threshold of detection and recognition for the four taste modalities (bitter, sweet, sour, salty) and reduced plasma zinc concentration, especially in patients treated with captopril for more than 6 months. This is not always associated with subjective complaints of taste disturbance.[12] In one report, patients who had such side effects tended to have lower plasma zinc concentrations than patients without side effects.[13] On the other hand, O'Connor *et al.*[14] did not observe changes in serum zinc or copper in seven patients treated with captopril 50 mg daily for 5–6 months.

Taste disorders and rash usually disappear when a non-sulphydryl ACE inhibitor is substituted for captopril, although the opposite has also been observed in one patient (i.e. disappearance of rash due to enalapril when replaced with captopril).[15,16]

Beneficial effects have also been attributed to the sulphydryl moiety. Sulphydryl-containing ACE inhibitor molecules form reversible disulphide links with themselves and with other sulphydryl-containing compounds and can serve as a depot form of the drugs.[17] In addition, activation of phospholipase and increased renal prostaglandin levels, elevated ventricular fibrillation threshold, reduction of reperfusion arrhythmias, increased coronary blood flow, decreased infarction size, and decreased myocardial stunning have all been reported with the use of captopril.

It has been suggested that the decreased myocardial stunning observed with captopril is in part due to free radical scavenging by the sulphydryl group. However, both ramipril and perindopril, ACE inhibitors that do not contain a sulphydryl group, have been shown to decrease ventricular fibrillation and increase coronary blood flow.[18,19] In the isolated rat heart, coronary blood flow increases after administration of captopril, but this also occurs with the *R,S*-isomer of captopril, with cysteine and with glutathione—compounds without ACE inhibitory activity. The increase in coronary flow produced by ramipril is smaller and delayed. These data have been interpreted as implying that captopril causes a more pronounced increase in coronary blood flow due to the sulphydryl group while ramipril causes a lesser increase due to the ACE inhibitory activity, probably related to increased prostaglandin levels.[20] In contrast intracoronary administration of enalapril in man has been shown to increase coronary blood flow despite a lower heart rate and blood pressure product that would be expected to lower coronary flow by autoregulation.[21] Thus the coronary vasodilatory effect of ACE inhibitors is at least partially independent of the sulphydryl group.

Prodrugs

Prodrugs have been developed in order to enhance the poor absorption of diacid ACE inhibitors. They are usually administered in esterified form and need to be activated after absorption.[22,23] Because of this, prodrugs usually have a slower onset and a longer duration of action than the respective active compounds. For example, alacepril, the prodrug of captopril, has a slower onset but longer duration of action.[24]

Most prodrugs currently available are hydrolysed to the active diacid compound in the liver, although this may also occur in other tissues. Disease at the site of activation may therefore have important implications for patients treated with a prodrug. Liver disease, such as cirrhosis, is known to affect the time course and efficiency of bioactivation of enalapril and other prodrugs. On the other hand, absorption of the parent drug may be enhanced in cirrhosis. Thus, the area under the concentration-time curve of the prodrug may be increased while that of the active (diacid) compound may be unchanged compared with normal. In addition, cirrhosis is associated with increased variability of both absorption and bioactivation.

In patients with severe CHF, with impaired hepatic blood flow and liver function, bioactivation of enalapril is delayed.[25] In normal subjects the peak concentration of the active diacid compound (enalaprilat) occurs approximately 4 h after oral administration of enalapril. In patients with significant CHF, however, bioactivation is delayed and peak concentrations of the active compound occur 2 h later (6 h after ingestion). In addition to this delayed bioactivation, absorption of enalapril is delayed in patients with CHF and serum concentrations of enalaprilat are consistently higher than in normal subjects. This may be due to a decreased volume of distribution, accompanied by a decrease in plasma clearance.

The speed of bioactivation of different prodrugs may vary and may also affect the onset of action. For example, cilazapril is activated rapidly while enalapril is activated at a slower rate.

Other than enhanced absorption, no extra beneficial effects of prodrugs have been reported, although theoretically prodrugs that are activated at specific sites may offer the potential for selectivity of action (i.e. drug targeting). Of the currently available ACE inhibitors, only enalapril is a prodrug.

Potency

Another important parameter by which ACE inhi-

bitors may be differentiated is potency. In addition to enabling a comparison between ACE inhibitors, measurements of potency are useful for screening new compounds and for the measurement of plasma concentrations of ACE inhibitors. Potency may be assayed by measuring the dissociation constant (K_i) of the enzyme to the inhibitor. A low dissociation constant indicates high potency; the enzyme is tightly bound to the inhibitor.[10] This method of measuring potency is not suited to very potent ACE inhibitors,[26] as a steady-state kinetic approach is very difficult for these drugs.

Most methods for measuring potency are based on enzymatic kinetic techniques usually using simple synthetic substrates, and measuring the products of the reaction with fluorimetric, isotopic or spectrophotometric techniques. IC_{50}, the concentration of ACE inhibitor that is capable of inhibiting 50% of the activity of the enzyme, is thus used as an index of potency.[27] Another way of assessing potency is by radioinhibitor binding displacement assay. This method measures the displacement of a potent radioligand ACE inhibitor (e.g. MK-351A, the tyrosyl analogue of lisinopril) by the ACE inhibitor under study.[28] A potent ACE inhibitor displaces the radioligand at a lower concentration than a weak one. This method can be used to measure directly the affinity of the ACE inhibitor to the enzyme and compare potency of ACE inhibitors. In general, there is agreement about the relative potencies of ACE inhibitors as measured by different methods.[29] ACE inhibitor potency may be clinically relevant, since for similar elimination half-lives, more potent ACE inhibors have a longer duration of action, allowing once-daily administration. In addition, on a theoretical basis it is possible that fewer drug interactions will occur with potent ACE inhibitors than with weak ones. Of the currently marketed compounds, lisinopril is the most potent.

Pharmacokinetic properties

These properties are important in determining the clinical use of ACE inhibitors. The duration of action has attracted much attention, especially concerning administration of these drugs to patients with CHF. In a comparison of captopril with enalapril, Packer *et al.*[30] administered fixed high doses of ACE inhibitors to patients with severe CHF who were on diuretics and digitalis. The long-acting ACE enzyme inhibitor enalapril produced a continuous depression of blood pressure without recovery of the pressure prior to the next does. This flat blood pressure-lowering curve was associated with a higher incidence of side effects, especially CNS and kidney effects, as compared to short-acting captopril which allowed partial recovery of the blood pressure before each dose.

On the other hand, ACE inhibitors with a long duration of action have proved beneficial in patients with CHF. In a randomised trial lisinopril, which has a longer duration of action than either captopril or enalapril, was found to increase exercise tolerance to a similar or more pronounced degree than captopril.[31] This was also associated with a slight increase in renal side effects.

Moreover, in the CONSENSUS trial, a randomised trial of enalapril versus placebo in patients with severe CHF, this long-acting ACE inhibitor was found to decrease mortality.[32] Thus, ACE inhibitors with a long duration of action are effective in patients with CHF. Similarly, in patients with hypertension, a long duration of action would appear to be a desirable attribute since it enables once-daily therapy.

Tissue effects

Several lines of evidence support the opinion that, in addition to the endocrine renin-angiotensin system, there is a tissue (paracrine, autocrine) or cellular (intracrine) renin-angiotensin system with physiological and pharmacological significance.[33–37] The lipophilicity or hydrophilicity of an ACE inhibitor may be an important factor determining penetration to different tissues, particularly the brain. Although individual ACE inhibitors may penetrate different tissues to a slightly different extent, as yet there is no evidence of a clinically relevant difference in tissue effects among the various ACE inhibitors. On the other hand, such differences may indeed emerge. It is also possible that the future use of prodrugs may enable local, selective activation in specific tissues.

Side effects

Although ACE inhibitors are remarkably well-tolerated compounds, they may cause significant side effects in susceptible individuals. Class-related side effects due to ACE inhibition include hypotension, hyperkalaemia, renal insufficiency, cough and angioedema. Nevertheless, as mentioned previously, the presence of a sulphydryl group may be associated with additional or more frequent side effects of certain types, such as skin rashes and taste disturbances. As experience with the drug class continues to grow, idiosyncracies to individual compounds may also emerge.

Additional pharmacological properties

ACE inhibitors with additional pharmacological properties may be synthesised. DeForrest *et al.*[38] synthesised a series of ACE inhibitors that were a combination of captopril and a thiazide diuretic and had potent diuretic properties in addition to their ACE inhibitory activity. The nature of the bridge between two compounds was found to alter the biological activity of the hybrid. Although the presence of a single molecule with dual properties may offer theoretical advantages from a pharmacokinetic point of view, low bioavailability and other considerations make these compounds less than ideal, and their development appears to have stopped.

Drug interactions

ACE inhibitors as a class exhibit interactions with other agents, such as enhancement of the antihypertensive effect of diuretics and beta-blockers. In addition individual ACE inhibitors may have specific interactions, such as the interaction of captopril (but not enalapril or lisinopril) with digoxin; decreased digoxin clearance has been reported in patients with CHF treated with captopril. In addition, food lowers the bioavailability of captopril but not of lisinopril or enalapril. All ACE inhibitors reduce the clearance of lithium; this interaction may enhance the risk of lithium toxicity in patients receiving these salts.

Cost

Cost is an important consideration when common chronic diseases such as hypertension are considered in a climate of fiscal constraint. Pricing structure depends on the setting (hospital, or outpatient), type of purchase (bulk or retail), the individual country under consideration, clinical use, the regulatory climate and other factors. Clear-cut differences between the three currently available ACE inhibitors are not apparent, although these drugs as a class are more expensive than some older antihypertensive agents, such as diuretics.

Conclusions

As the number of ACE inhibitors increases, it is becoming apparent that they may be differentiated by a number of criteria, including chemical structure, potency, pharmacokinetics, effects on tissue ACE, side effects, and whether the drug is directly acting or requires bioactivation from a prodrug form.

Chemical structure, notably the group which functions as a zinc ligand is important. The sulphydryl group of captopril is associated with taste and skin disorders but, conversely, certain beneficial effects, e.g. on reperfusion injury, have been attributed to this chemical group in captopril.[4]

Prodrugs must be activated, usually by hydrolysis in the liver, after absorption. In the case of concomitant disease at the site of bioactivation (e.g. cirrhosis) or decreased blood flow (e.g. CHF), increased variability of blood concentrations and delayed onset of action may occur.

High potency enhances the duration of action, allowing once-daily dosing, and, in theory, may result in a reduced probability of non-pharmacological drug interactions.

Pharmacokinetic properties, especially half-life, are also important. A long duration of action is preferable in the treatment of hypertension. Controversy surrounds the merits of a long duration of action in the treatment of CHF, as high fixed doses of enalapril have caused more persistent lowering of blood pressure and more CNS and renal dysfunction than captopril. However, in other studies, enalapril has been found to reduce mortality in patients with severe CHF, and results with lisinopril demonstrate sustained clinical and haemodynamic improvement.

Inhibition of tissue ACE is now believed to play a role in the clinical effects of ACE inhibitors. Differences in tissue affinity, lipophilicity or hydrophilicity, kinetics and bioactivation may provide additional parameters for differentiation of ACE inhibitors in the future.

Additional pharmacological properties. ACE inhibitors with diuretic activity were synthesised but did not reach the stage of clinical development.

Side effects. Although class side effects (hypotension, renal insufficiency, hyperkalaemia, cough, angioedema) are common to all ACE inhibitors, the presence of a sulphydryl group has been associated with more frequent occurrence of skin rash and taste disturbances.

Similarly, in addition to class-related drug interactions (e.g., enhancement of the antihypertensive effect of diuretics), drug-specific interactions have been reported (e.g. reduced digoxin clearance with captopril).

Cost is an important consideration in treating chronic disorders such as hypertension, but does not differ significantly among the ACE inhibitor class.

Currently, duration of action, the presence of a sulphydryl group, and the need for bioactivation form the most clinically relevant differences between ACE inhibitors.

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